

REMARKS

Claim Amendments

Claims 1-37 have been canceled. Claims 38-40 have been added. The newly added claims do not add or constitute new matter. Support for the newly added claims may be found throughout the specification and originally filed claims. More particularly, support for the transgenic mouse and methods of using the transgenic mouse as recited in the newly added claims may be found, for example, at page 4, lines 19-31, at page 5, lines 1-9, page 10, line 12 through page 16, line 30, at page 52, lines 20-31, and at page 54, lines 5-15, of the specification. As such, no new matter has been added.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 38-40 are pending in the instant application.

Applicant respectfully requests reconsideration of the application in view of the amendments and remarks made herein.

Specification

In the Office Action, mailed December 24, 2003, see page 2), the Examiner has objected to the specification because the first line of the specification should state the application claims priority to U.S. Provisional Applications Nos. 60/218,074, filed July 12, 2000, and 60/243,958, filed October 26, 2000. Applicant is unsure of the reason for this objection, in that it appears the first paragraph of the originally filed specification does make a claim of priority to the two applications (see page 1 of the specification, first full paragraph, under the heading "Related Applications"), and the priority claim was also made on the transmittal filed with the application. Applicant believes that the priority claim has been properly made, and requests that the objection be withdrawn, or further guidance be given.

Further, the Examiner has objected to the specification because the description of Figures 2A-2B should clearly state the sequence shown is SEQ ID NO:1. Applicant submits that such a correction to the specification has already been made. More particularly, Applicant filed a

preliminary amendment on December 4, 2002, which amendment included a description of Figures 2A-2B identifying the sequence disclosed in Figure 2A as SEQ ID NO:1. The December 4 amendment was made originally in response to a Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence or Amino Acid Sequence Disclosures, mailed October 3, 2002, and further in response to an Office Action mailed November 15, 2002, which requested the above-referenced changes be made. Therefore, Applicant submitted the December 4 amendment. Applicant submits that he has already complied with the Examiner's request, and that the Application is in compliance with the sequence rules. For the Examiner's convenience, a copy of the preliminary amendment is attached herewith.

Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 8, 11, 12, 17-26, 28 and 30-32 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicant respectfully traverses the rejection. However, Applicant believes the rejection has been overcome in light of the amendments made herein and arguments presented below.

Claims 8, 11, 12, 17-26, 28 and 30-32 have been canceled. New claims 38-40 are drawn to a transgenic mouse whose genome comprises a disruption in an MC3-R gene comprising the sequence set forth in SEQ ID NO:1, which disruption results in a phenotype of passive behavior or decreased attempts to escape, and to a method of using the mouse to identify agents capable of modulating the phenotypes.

The specification has demonstrated that disruption of the gene comprising SEQ ID NO:1 results in a specific phenotype, in particular, a phenotype of passive behavior or a decrease in number of escape attempts. Several potential and credible uses for the transgenic mice have been disclosed in the specification, such as, for example, as a model for conditions or disorders associated with disruption of the gene, such as the passive behavior or decrease in escape attempts exhibited by the transgenic mice (see, for example, page 20, lines 16-31 and page 21, lines 1-28 of the specification). Other asserted uses for the claimed mice include, but are not limited to, use as models for dysfunctions or disease (*e.g.* a model of passive behavior), for identifying agents that ameliorate disease symptoms, for identifying agents that affect or modulate a phenotype caused by the gene disruption, such as the phenotypes claimed, or for determining the specificity of an agent targeting the gene comprising the sequence set forth in SEQ ID NO:1.

Applicant submits that the utilities asserted for the claimed mouse are well-established in the art and would be immediately apparent to the skilled artisan, even absent Applicant's disclosure. This is a result of the establishment of transgenic knockout mice, such as those described in and claimed by the instant application, as valuable tools for determining the function of genes. In the present case, the transgenic mouse described in the instant specification would be recognized by the skilled artisan as revealing the physiological role of the target MC3-R gene comprising SEQ ID NO:1 in conditions and disorders related to the phenotypes disclosed, specifically passive behavior and decreased escape attempts. Therefore, the potential uses asserted above and in the specification would be recognized by the skilled artisan as substantial and credible, and would be considered specific to the claimed transgenic mouse. The value of such an *in vivo* model would be immediately apparent, as supported by the homology between the mouse and human genomes, and the general acceptance that gene function in the mouse is related to and representative of that of humans.

The utility of transgenic knockout mice, and in particular mice exhibiting a phenotype such as the claimed mice, is well-established in the art. In the process of drug discovery, mouse models are routinely used as an *in vivo* screening model to test potential therapeutic agents that have passed through one or more initial *in vitro* (or *in vivo*) screening tests. Mouse models, including knockout transgenic mice, representing various conditions or disorders are used for such purposes. A mouse model for passive behavior or decreased escaping, such as that of the present invention, would clearly be considered useful as a tool for screening agents thought to have the potential to affect or modulate such abnormal behaviors.

Applicant submits that in order to satisfy the utility requirements set forth in 35 U.S.C. § 101, the specification must assert a specific and substantial utility that is credible to a skilled artisan, or the utility of the claimed invention must be apparent to the skilled artisan. See MPEP § 2107. Applicant submits that the instant specification satisfies these requirements, particularly with respect to the invention recited in newly submitted claims 38-40. Although Applicant believes that the phenotype exhibited by the claimed mice has been shown to be related to and/or linked to a human condition or disorder, Applicant is not aware of any such requirement in order to establish patentable utility. In fact, as noted above, Applicant submits that a phenotype desired to be modulated by the skilled artisan, such as the behavioral abnormalities seen in the claimed

mice, should be sufficient to demonstrate that the transgenic mouse possesses a substantial utility specific to the claimed mouse.

Even in the absence of a link between the phenotype(s) of the claimed mouse and a human disease or disorder, a link between the disruption in SEQ ID NO:1 and the claimed phenotype **in a mouse** has been clearly established. The transgenic mouse could be used to study or investigate the abnormal behaviors related to disruption of this sequence in a mouse, and to discover or develop treatments in mice or related animals. These are clearly “real world” uses for the claimed transgenic mice that satisfy the utility requirements set forth in 35 U.S.C. § 101.

Applicant believes that the rejection under 35 U.S.C. § 101 for lack of a specific or substantial utility has been shown to be improper. Applicant has asserted in the specification several specific and substantial uses for the claimed transgenic mice, described above. Further, in light of the art-recognized value of and demand for transgenic knockout mice, the asserted utilities are among many that are well-established and credible to the skilled artisan. As a result, Applicant does not believe that the Examiner has properly established that the claimed invention lacks a specific and substantial utility.

The Examiner’s rejection of claims 8, 11, 12, 17-26, 28 and 30-32 is no longer relevant as a result of the cancellation of these claims. Applicant submits that the rejection does not apply to newly submitted claims 38-40 for the reasons set forth above. Therefore, withdrawal of the rejection under 35 U.S.C. § 101 is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has also rejected claims 8, 11, 12, 17-26, 28, and 30-32 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility set forth in the above utility rejection. Applicant respectfully traverses the rejection. However, for the reasons set forth above in response to the utility rejection, Applicant submits that the rejection under 35 U.S.C. § 112, first paragraph, for lack of utility has been overcome. Therefore, Applicant respectfully requests withdrawal of the rejection.

The Examiner has also asserted that the specification does not reasonably provide enablement for the transgenic mouse as claimed. The Examiner’s enablement rejection relates to the unpredictability of a phenotype in a transgenic mouse or non-human animal, and the state of the art of embryonic stem cell technology related to gene disruption, which is limited to the mouse

system. The Examiner further alleges that the claims do not provide a nexus between disruption in the disrupted target gene and the phenotype exhibited by the claimed mice. Applicant traverses each aspect of the rejection. However, the rejection has been overcome by the cancellation of claims 8, 11, 12, 17-26, 28, and 30-32.

Applicant has submitted new claims 38-40, which overcome the Examiner's enablement rejection. More particularly, the invention as recited in these claims addresses each of the Examiner's concerns by: (1) reciting a transgenic mouse, (2) reciting a detectable, useful phenotype resulting from disruption of the target MC3-R gene, and/or (3) cancellation of the claim(s). Therefore, Applicant has overcome the rejection under 35 U.S.C. § 112, first paragraph, for enablement, and requests its withdrawal.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 8, 11, 12, 17-26, 28, 30-32 under 35 U.S.C. § 112, second paragraph, for being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses the rejection. Claims 8, 11, 12, 17-26, 28, 30-32 have been canceled, and the rejection is no longer relevant to these claims.

In one aspect, the Examiner asserts that the meaning of "MC3-R" genes cannot be determined. Applicant disagrees that the skilled artisan would not be aware of what genes this term encompasses, particularly in light of Applicant's disclosure. However, claims 38-40 clearly recite the gene or sequence disrupted in the present invention.

According to the Examiner, claims 17-26 are allegedly indefinite in that they do not clearly set forth that the disruption in the MC3-R gene causes the phenotype claimed. Applicant traverses the rejection. However, new claims 38-40 clearly recite that the phenotype exhibited by the claimed mice is a result of disruption of the MC3-R gene.

With regard to claim 21, the Examiner asserts the claim is indefinite because it is not stated that the decrease in passivity is over a period of time or in comparison to a wild-type control. Claim 21 is cancelled, and the pending claims recite passive behavior as relative to a wild-type control mouse.

Regarding claim 22, the Examiner has asserted that the metes and bounds of the term "hypoactivity" cannot be determined. Applicants disagree. However, this term is no longer recited in the pending claims.

Regarding claim 23, the claim is considered indefinite because it is unclear whether the decrease is over a period of time or in comparison to a wild-type control. Applicant has cancelled claim 23. The rejection is not relevant to the pending claims in that these claims recite to what the decrease is relative.

Applicant submits that the rejection under 35 U.S.C. § 112, second paragraph, has been overcome by the cancellation of claims. Therefore, Applicant respectfully requests withdrawal of the rejection. Applicant submits that new claims 38-40 clearly point out and distinctly claim that regarded as the invention as required by the second paragraph of 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 102.

Claims 8, 11, 12, 17-26, 28 and 30-32 have been rejected by the Examiner under 35 U.S.C. § 102(a) as being anticipated by Butler *et al.* (*Endocrinology* (September 2000) Vol. 141, Pages 3518-3521). Applicant respectfully traverses the rejection. However, as claims 8, 11, 12, 17-26, 28 and 30-32 have been cancelled, the rejection is no longer relevant.

To anticipate a claim, the reference must teach every element of the claim. **“A claim is anticipated [under §102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”** MPEP §2131 *citing* (*Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

According to the Examiner, Butler teaches male mice with a homozygous disruption in an MC3-R gene with reduced energy expenditure as determined by reduced wheel running behavior, which the Examiner asserts is considered hypoactive and passive. The Examiner asserts that the Butler mouse inherently does not attempt to escape and has kidney abnormalities as it was produced by the method described in the specification.

Claims 38-40 recite a transgenic mouse comprising a homozygous disruption in an MC3-R gene comprising SEQ ID NO:1, wherein the disruption is produced using a targeting construct comprising the sequences set forth in SEQ ID NO:3 and SEQ ID NO:4. Applicant submits that Butler *et al.* fails to teach each and every claim limitation as recited in new claims 38-40. More particularly, Butler *et al.* fails to teach the specific disruption produced in the transgenic mouse, and further does not teach that the disruption results in a phenotype of passive behavior or decreased escape attempts. Further, Butler *et al.* fails to teach the method of using a transgenic

mouse comprising the disruption in order to identify agents capable of affecting these phenotypes. As such, the presently claimed invention is not anticipated by the disclosure of Butler *et al.*

In light of the cancellation of claims and remarks set forth above, Applicant has overcome the rejection under 35 U.S.C. § 102(a), and respectfully requests withdrawal of the rejection.

Rejection under 35 U.S.C. § 103

Claims 8, 11, 12, 28 and 30-32 were rejected as being unpatentable under 35 U.S.C. § 103(a) based upon the teachings of Huszar, 1997, *Cell*, Vol. 88, pages 131-141, in view of Desarnaud, 1994, *Biochem. J.*, Vol. 299, pages 367-373. Applicant respectfully traverses this rejection.

According to the Examiner, Huszar teaches making a mouse having a disruption in an MC4-R gene. However, the Examiner concedes that Huszar fails to teach disruption of the gene targeted in the instant invention, particularly the MC3-R gene, and more particularly the MC3-R gene comprising the sequence set forth in SEQ ID NO:1, as recited in the pending claims.

Desarnaud simply discloses the nucleic acid sequence of the mouse MC3-R gene. However, Desarnaud clearly fails to teach or suggest any transgenic mouse comprising disruptions in any gene, particularly the MC3-R gene comprising the sequence set forth in SEQ ID NO:1. Further, Desarnaud fails to teach a phenotype resulting from such disruption of the MC3-R gene as presently claimed.

As a basis of the obviousness rejection under 35 U.S.C. § 103, the Examiner asserts that one of ordinary skill in the art would have been motivated to produce a transgenic mouse having a disruption in a melanocortin gene as described by Huszar wherein the melanocortin gene was MC3-R as taught by Desarnaud. One of ordinary skill in the art would have been motivated to disrupt the MC3-R gene in place of the MC4-R gene in order to study the function of this gene *in vivo*. The Applicant respectfully disagrees. However, in light of the cancellation of claims, the rejection is no longer relevant. The Applicant submits that the rejection does not apply to claims 38-40.

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) must **teach or suggest all the claim limitations**. See MPEP §2143. The Applicant contends that the prior art references cited by the Examiner are not sufficient to establish the

presently claimed invention as *prima facie* obvious. More particularly, the disclosures of Huszar and Desarnaud, alone or in combination, fail to teach all of the limitations as recited in claims 38-40. Huszar provides no disclosure or teaching of the specific melanocortin receptor gene described in the instant specification, and in particular does not disclose a phenotype exhibited by transgenic mice as a result of disruption of said gene, particularly a phenotype of passive behavior or decreased escape attempts, as claimed by the present invention. Likewise, Desarnaud does not provide any teaching or suggestion relating to a disruption in the mouse MC3-R gene as presently claimed, nor to disruption of any gene, particularly disruption resulting in the claimed phenotype.

Taken together, the disclosures Huszar and Desarnaud are devoid of any teaching or suggestion of the transgenic mice and cells as recited in the pending claims. More particularly, the combined disclosures of Huszar and Desarnaud do not teach or suggest in any way transgenic mice whose genomes comprise disruptions in an MC3-R gene comprising the sequence set forth in SEQ ID NO:1, wherein such transgenic mice exhibit a phenotype of passive behavior or decreased escape attempts. Each of these references do not make up for the deficiencies found in the other.

As the rejection of claims 8, 11, 12, 28 and 30-32 under 35 U.S.C. § 103 is no longer relevant, and new claims 38-40 are not obvious in view of the sole or combined teachings of Huszar and/or Desarnaud, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-653.

Respectfully submitted,

Date: _____

May 24, 2004

Kelly L. Quast

Kelly L. Quast, Reg. No. 52,141

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USPTO RECEIPT FOR INDICATED ITEMS

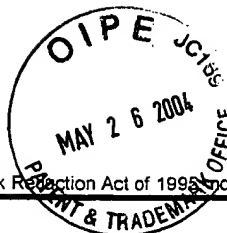
Appln. No: 09/903,395
Inventor: Allen
Title: Transgenic Mice Containing Melanocortin-3 Receptor Gene Disruptions

Agent: JKB
Date: Dec. 4, 2002
Docket No.: R-365

ENCLOSED:

- Preliminary Amendment/Response to PTO Notice mailed 11/15/02
- Transmittal Form PTO/SB/21
- PTO Notice mailed November 15, 2002
- New Figure 2A and marked-up copy of same
- Certificate of Mailing Under 37 CFR 1.8





PTO/SB/21 (08-00)

Approved for use through 10/31/2002. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09.903,395
Filing Date	July 10, 2001
First Named Inventor	Keith D. Allen
Group Art Unit	1632
Examiner Name	Michael C. Wilson
Attorney Docket Number	R-653

Total Number of Pages in This Submission 8

ENCLOSURES (check all that apply)

- | | | |
|--|---|--|
| <input type="checkbox"/> Fee Transmittal Form | <input type="checkbox"/> Assignment Papers (for an Application) | <input type="checkbox"/> After Allowance Communication to Group |
| <input type="checkbox"/> Fee Attached | <input checked="" type="checkbox"/> Drawing(s) New Fig. 2A | <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences |
| <input checked="" type="checkbox"/> Amendment/Reply Preliminary | <input type="checkbox"/> Licensing-related Papers | <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) |
| <input type="checkbox"/> After Final | <input type="checkbox"/> Petition | <input type="checkbox"/> Proprietary Information |
| <input type="checkbox"/> Affidavits/declaration(s) | <input type="checkbox"/> Petition to Convert to a Provisional Application | <input type="checkbox"/> Status Letter |
| <input type="checkbox"/> Extension of Time Request | <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address | <input type="checkbox"/> Other Enclosure(s) (please identify below): |
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| <input type="checkbox"/> Information Disclosure Statement | <input type="checkbox"/> Request for Refund | |
| <input type="checkbox"/> Certified Copy of Priority Document(s) | <input type="checkbox"/> CD, Number of CD(s) _____ | |
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| <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53 | | |

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Robert J. Driscoll, Reg. No. 47,536
Signature	
Date	December 4, 2002

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date:

12/4/02

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Date

12/4/02

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,395	07/10/2001	Keith D. Allen	R-653	9465

7590

11/15/2002

DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

EXAMINER

WILSON, MICHAEL C

ART UNIT

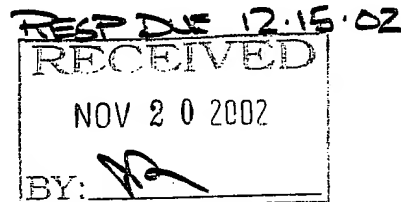
PAPER NUMBER

1632

DATE MAILED: 11/15/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.





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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER
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9

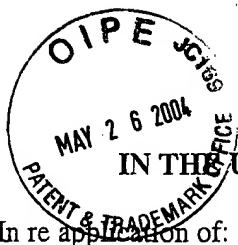
DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

The reply filed on 11-7-02, paper number 9, is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): a marked up version of Figure 2A has not been provided. In addition, it would be more efficient for applicants to get a draftsman's review of the drawings before amending Figure 2A. To comply with the Sequence rules as required in the office action sent 10-2-03, paper number 7, applicants should insert a sentence describing Figure 2A as containing SEQ ID NO:1 into the description of Figure 2A-2B on page 9, line 25. After "hormone receptor genes." insert a description of Fig. 2A, e.g. - Figure 2A shows... (SEQ ID NO:1).-- See 37 CFR 1.111. Since the above-mentioned reply appears to be bona fide, applicant is given ONE (1) MONTH or THIRTY (30) DAYS from the mailing date of this notice, whichever is longer, within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a).

MICHAEL C. WILSON
PATENT EXAMINER



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Keith D. ALLEN

Application No.: 09/903,395

Filed: July 10, 2001

For: Transgenic Mice Containing
Melanocortin-3 Receptor Gene
Disruptions

Examiner: Michael C. Wilson

Art Unit: 1632

Atty. Docket No.: R-653

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to the examination of the above-referenced application and in response to the U.S. Patent Office Notice mailed November 15, 2002, entry of the following amendment is respectfully requested:

In the Specification

Please replace the paragraph on page 9, lines 24-27, with the following paragraph:

--Figure 2 (Panels A and B) shows design of the targeting construct used to disrupt melanocortin-3 receptor genes. Figure 2 (Panel A), which illustrates the target sequence (SEQ ID NO:1) for the targeting construct, shows the location and extent of the disrupted portion of the melanocortin-3 receptor genes, as well as the nucleotide sequences flanking the Neo' insert in the targeting construct. Figure 2 (Panel B) shows the sequences identified as SEQ ID NO:3 and SEQ ID NO:4, which were used as the targeting arms (homologous sequences) in the melanocortin-3 receptor targeting construct.--

In the Drawings

Please replace Figure 2A in the application with the enclosed new Figure 2A. A marked-up copy of Figure 2A is also enclosed, with corrections indicated in red.

REMARKS

The foregoing amendment to the specification is supported in Figure 2A as originally filed and does not introduce new matter.

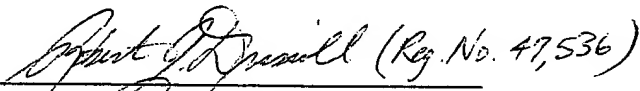
The amendment to Figure 2A merely adds a sequence identifier to the figure to comply with 37 C.F.R. 1.821(d) and does not introduce new matter.

Enclosed is a marked-up version of the changes made by this amendment. The enclosed pages are captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**

Entry of the foregoing amendment is respectfully requested and favorable action on the merits is earnestly solicited.

Date: December 4, 2002

Respectfully submitted,

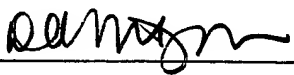

for Jane K. Babin, Reg. No. 47,224

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CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence and its listed enclosures is being deposited with the United States Postal Service as First Class Mail, postage paid, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on December 4, 2002

Name: Deborah A. Mojarro

Signed: 

Date: 12/4/02

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 9, lines 24-27 have been amended as follows:

Figure 2 (Panels A and B) shows design of the targeting construct used to disrupt melanocortin-3 receptor genes. Figure 2 (Panel A), which illustrates the target sequence (SEQ ID NO:1) for the targeting construct, shows the location and extent of the disrupted portion of the melanocortin-3 receptor genes, as well as the nucleotide sequences flanking the Neo' insert in the targeting construct. Figure 2 (Panel B) shows the sequences identified as SEQ ID NO:3 and SEQ ID NO:4, which were used as the targeting arms (homologous sequences) in the melanocortin-3 receptor targeting construct.



Underlined = deleted in targeting construct

Bold = sequence flanking Neo insert in targeting construct

TCTAGACTGGACAGCATCCACAAGAGAAGCACCTAGAAGGAGAATTTTCCCCAGCAGCTT
GCTCAGGACCCTGCAGGAGCCGCAGCTGGGACTGGACCTGCTGTAAACCATGAACTCTTC
CTGCTGCCTGTCTTCTGTTTCTCCGATGCTGCCTAACCTCTCTGAGCACCCCTGCAGCCCC
TCCTGCCAGCAACCGGAGCGGCAGTGGGTTCTGTGAGCAGGTCTTCATCAAGCCGGAGGT
CTTCCTGGCTCTGGGCATCGTCAGTCTGATGGAAAACATCCTGGTGATCCTGGCTGTGGT
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CATGCTGGTGAGCCTGTCCAACCTCCCTGGAGACCATCATGATCGCCGTGATCAACAGCGA
CTCCCTGACCTTGGAGGACCAGTTTATCCAGCACATGGATAATATCTTCGACTCTATGAT
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CACCATCTTCTATGCCCTTCGGTACCACAGCATCATGACAGTTAGGAAAGCCCTCACCTT
GATCGGGGTCTCTGGGTCTGCTGCGGCATCTGCGGCGTGATGTTTCATCATCTACTCCGA
GAGCAAGATGGTCATCGTGTGTCTCATCACCATGTTCTTCGCCATGGTGCTCCTCATGGG
CACCCATATATATCCACATGTTCTCTTCGCCAGGCTCCACGTCCAGCGCATCGCAGTGCT
GCCCCCTGCTGGCGTGGTGGCCCCACAGCAGCACTCCTGCATGAAGGGGGCTGTCACCAT
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CATCATCACCTGCCCCACCAATCCCTACTGCATCTGCTACACGGCCCATTTCAACACCTA
CCTGGTTCTCATCATGTGCAACTCCGTTCATCGACCCCCCTCATCTACGCCTTCCGCAGCCT
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GCAGACGGGACACGGCGTAGGATGGGCTGTCTGTGAGGATCTGTGTGTGGGTAAGTCAGT
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TGCTTCAAGCCAACCAGACCGGAGGGCTCTCGTGAGCAGAAAGAGTGCTTAGACTTCCGG
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CTTACATCTGTGCCAGCCTCCCCGAACCCCTGCACAGAGACATGACCCCTTCTCCCTGT
GCCGTTGTCATGGTTGTTATTATTGTTGGAGTTTTGTTTCGTTAAAATCTAAGCTT
(SEQ ID NO:1)

FIGURE 2A



Underlined = deleted in targeting construct

Bold = sequence flanking Neo insert in targeting construct

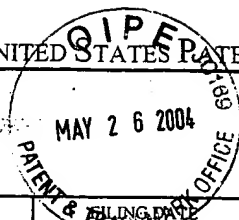
TCTAGACTGGACAGCATCCACAAGAGAAGCACCTAGAAGGAGAATTTTCCCCAGCAGCTT
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TCCTGCCAGCAACCGGAGCGGCAGTGGGTTCTGTGAGCAGGTCTTCATCAAGCCGGAGGT
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CTTACATCTGTGCCAGCCTCCCCGAACCCCTGCACAGAGACATGACCCCTTCTCCCTGT
GCCGTTGTTCATGGTTGTTATTATTGTTGGAGTTTTGTTTCGTTAAAATCTAAGCTT

(SEQ ID NO:1)

FIGURE 2A



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,395	07/10/2001	Keith D. Allen	R-653	9465

7590 11/24/2003
DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

EXAMINER

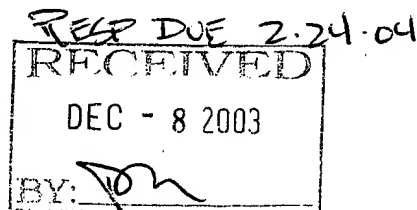
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 11/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.



Office Action Summary



Application No.

09/903,395

Applicant(s)

ALLEN, KEITH D.

Examiner

Michael C. Wilson

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above claim(s) 1-7, 9, 10, 13-16, 27, 29 and 33-37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8, 11, 12, 17-26, 28 and 30-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11-21-01 6) ☐ Other:

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DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group III, claims 8, 11, 12, 17-26, 28 and 30-32, filed 7-22-03 is acknowledged.

Claims 1-7, 9, 10, 13-16, 27, 29 and 33-37 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Specification

The specification is objected to because the first line of the specification should state the application claims priority to US Provisional Application No: 60/218,074, filed 7-12-00 and 60/243,958, filed 10-26-00.

The application numbers throughout the specification will require updating as necessary.

The description of Fig. 2A-2B should clearly state the sequence shown is SEQ ID NO:1.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 8, 11, 12, 17-26, 28 and 30-32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 8, 17-26 and 28 are directed toward a non-human transgenic animal, specifically a mouse, having a disruption of an MC3-R gene. Claims 11, 12 and 30-32 are directed toward using a non-human transgenic animal, specifically a mouse, having a disruption of an MC3-R gene. The specification teaches making MC3-R $-/-$ mice having only one kidney (pg 54, line 5-10). However, the strain of mice used spontaneously has only one kidney (pg 54, line 8). Therefore, the specification states it cannot be determined whether the lack of a kidney correlates to the disruptions in MC3-R (pg 54, lines 9-10). As such, a mouse with only one kidney does not have a use as claimed because it is not caused by the disruption in MC3-R or represent a disease state caused by a disruption in MC3-R. The specification suggests using the mice as a model of disease, specifically as a model for behavioral abnormalities, such as neurological, neuropsychological, psychotic phenotypes (pg 19-21; pg 21, lines 6-10). However, the specification does not disclose that behavioral abnormalities, specifically neurological, neuropsychological or psychotic disease found in humans, are linked to a disruption in MC3-R. Male MC3-R $-/-$ mice were passive, hypoactive and did not attempt to escape during examination. Female MC3-R $-/-$ mice were unremarkable (pg 54, lines 13-15). The specification does not provide any use for such a mouse, how such a mouse correlates to any disease, or that a disruption in MC3-R is found in hypoactive humans. None of the phenotypes described on pg 54 or claimed correlate

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to a useful phenotype because the phenotypes are not specific to a disease and are not linked to a disruption in an MC3-R gene in humans. The results of the tests are also not statistically significant because the number of mice tested is not disclosed. The mice claimed cannot be used to determine compounds that modulate MC3-R expression (e.g. claim 11) because MC3-R is not expressed in the mice. Using the mice to determine whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that ameliorate any condition using the mice. Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having a behavioral or renal abnormality as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 11, 12, 17-26, 28 and 30-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having a disruption in an MC3-R gene and a behavioral or renal abnormality.

The specification does not teach how to make animals or cells having a disruption in an MC3-R gene other than mice. The only means of making a non-human animal with a disruption in an MC3-R gene taught in the specification is by using mouse embryonic stem cell technology. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). Since the time of filing, Zan (Nature Biotech, 2003, Vol. 21, pg 645-651) taught making knockout rats using mutagenized male rats, which was not taught in the specification and considered essential to making knockout rats. The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of an MC3-R gene in non-mice, non-human species or correlate the MC3-R gene in mice to the MC3-R gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a transgenic, non-human animal or cells having a disruption in an MC3-R gene in any species other than mice.

The specification does not provide adequate correlation between the phenotype obtained in mice to the phenotype obtained in other species. The state of the art at the time of filing was that the phenotype of transgenic mice does not predict the phenotype in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human b₂-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the specification does not enable making transgenic having the disclosed phenotypes in species other than mice.

In addition, claims 17-26 do not provide a nexus between the disruption in MC3-R and the phenotypes claimed. The claims do not recite the disruption of MC3-R causes the phenotype claimed. The specification does not teach disrupting the MC3-R gene in mice already lacking production of MC3-R or in mice already having the phenotypes recited in claims 17-26. Given the art of transgenics at the time of filing taken with the guidance provided in the specification, the claim should reflect the fact that the phenotypes recited in claims 17-26 are a result of MC3-R disruption.

Otherwise, it would require one of skill undue experimentation to make the mouse as broadly claimed.

The specification does not enable using a transgenic with a wild-type phenotype as encompassed by claims 8, 11, 12, 28 and 30-32. The transgenics in the claims do not recite any phenotype and may, therefore, have any phenotype including wild-type phenotype. In particular, claims 30-32 only require determining whether a phenotype is present and do not require the mouse used has the phenotype. The specification does not provide any use for a transgenic having a disruption in an MC3-R gene that has a wild-type phenotype. The only disclosed phenotype for the transgenic claimed is one that correlates to a disruption in an MC3-R gene. Therefore, the claims should recite a non-wild-type phenotype that correlates to a disruption in an MC3-R gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 11, 12, 17-26, 28, 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants consider "MC3-R" genes cannot be determined. The specification defines the term as any gene of SEQ ID NO:1 or having homology to SEQ ID NO:1 (pg 8, lines 7-12). However, not all genes sharing homology with SEQ ID NO:1 are MC3-R genes. For example MC4-R shares homology with SEQ ID NO:1, and is not an MC3-R gene.

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Claims 17-26 are indefinite because they do not clearly set forth that the disruption in MC3-R causes the phenotype.

Claim 21 is indefinite because if the decrease in initiative ("passivity") is over a period of time or in comparison to a wild-type control.

The metes and bounds of what applicants consider "hypoactivity" cannot be determined (claim 22). The phrase is not defined in the specification and does not have an art recognized definition. The metes and bounds of what applicants consider "hypoactive" cannot be determined. How active is hypoactive?

Claim 23 is indefinite because if the decrease is over a period of time or in comparison to a wild-type control.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 8, 11, 12, 17-26, 28 and 30-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Butler (Sept. 2000, Endocrinology, Vol. 141, pg 3518-3521).

Provisional application 60/218,074 suggested a mouse having a disruption in SEQ ID NO:1 but did not teach the phenotype of the mouse. Specifically '074 did not teach that the mouse was passive, hypoactive or did not attempt to escape while being handled. As such, '074 supports claims 8 and 28, but not claims 17-26. The effective

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filing date of claims 17-26 as they relate to obtaining a mouse that was passive, hypoactive or did not attempt to escape while being handled is 10-26-00, the filing date of 60/243,958, which taught male homozygous mice were passive, hypoactive and did not attempt to escape while being handled (pg 69, last 3 lines). The effective filing date of claims 17-26 as they relate to having a kidney abnormality, reduced kidney size, unilateral renal agenesis, and decreased locomotion is the instant application, filed 7-10-01 because such limitations are not taught in the provisional applications.

Butler taught male mice with a homozygous disruption in the MC3-R gene had reduced energy expenditure as determined by reduced wheel running behavior (pg 3520, col. 1, last full ¶). Reduced wheel running is considered hypoactive and passive as claimed. The mice taught by Butler inherently do not attempt to escape and have the kidney abnormalities claimed because they were made using the method described in the specification. The disruption of the MC3-R gene in Butler is the same disruption disclosed in the instant application. Therefore, the phenotypes claimed are inherent in the mouse of Butler because the mouse of Butler has the same structure disclosed in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8, 11, 12, 28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huszar (Cell, Jan. 10, 1997, Vol. 88, pg 131-141) in view of Desarnaud (1994, Biochem. J., Vol. 299, pg 367-373).

Huszar taught making a mouse having a disruption in MC4-R gene. Huszar did not teach disrupting the MC3-R gene.

However, Desarnaud taught the nucleic acid sequence of the mouse MC3-R gene.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in melanocortin gene as taught by Huszar wherein the melanocortin gene was MC3-R as taught by Desarnaud. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the MC3-R gene instead of the MC4-R gene to determine the function of MC3-R *in vivo*.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120. The examiner's phone number will change on Jan. 12th, 2004 to 571-272-0738.

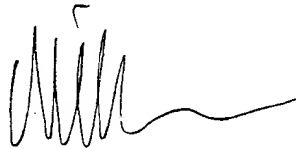
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Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

A handwritten signature in black ink, appearing to read 'Wilson', with a long horizontal flourish extending to the right.

**MICHAEL WILSON
PRIMARY EXAMINER**